


FORM PTO-1390 (REV 10-94)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 12875.18USWO
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) unknown 09/857752
INTERNATIONAL APPLICATION NO. PCT/DK99/00720	INTERNATIONAL FILING DATE 20 December 1999	PRIORITY DATE CLAIMED 21 December 1998	
TITLE OF INVENTION A METHOD AND AN APPARATUS FOR CUTTING OF TISSUE BLOCKS			
APPLICANT(S) FOR DO/EO/US SORENSEN et al.			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).</p> <p>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <p>a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</p> <p>b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau.</p> <p>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US)</p> <p>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <p>a. <input checked="" type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</p> <p>b. <input checked="" type="checkbox"/> have been transmitted by the International Bureau.</p> <p>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p>d. <input type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).</p> <p>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p> <p>Items 11. to 16. below concern document(s) or information included:</p> <p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>14. <input type="checkbox"/> A substitute specification.</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>16. <input checked="" type="checkbox"/> Other items or information: Preliminary Amendment, Marked-up Copy, Abstract Page, Form PCT/IPEA/409, 11 sheets of Formal Drawings, International Publication Page</p>			

U.S. APPLICATION NO (If known, see 37 CFR 1.5) unknown 09/857752		INTERNATIONAL APPLICATION NO PCT/DK99/00720		ATTORNEY'S DOCKET NUMBER 12875.18USWO	
17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)): Search Report has been prepared by the EPO or JPO.....\$860.00 International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)).....\$690.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))\$710.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO \$1000.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)\$100.00				CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$860.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	39 -20 =	19	X \$18.00	\$342.00	
Independent claims	2 -3 =	0	X \$80.00	\$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$260.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$1202.00	
Reduction by 1/2 for filing by small entity, if applicable. Small entity status is claimed pursuant to 37 CFR 1.27				\$601.00	
SUBTOTAL =				\$601.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+ \$	
TOTAL NATIONAL FEE =				\$601.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				+ \$	
TOTAL FEES ENCLOSED =				\$601.00	
				Amount to be:	
				refunded	\$
				charged	\$
a. <input checked="" type="checkbox"/> Check(s) in the amount of <u>\$601.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-2725</u> .					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO John J. Gresens MERCHANT & GOULD P.O. Box 2903 Minneapolis, MN 55402-0903					
				SIGNATURE: 	
				NAME: John J. Gresens	
				REGISTRATION NUMBER: 33,112	

09/857752

531 Rec'd PCT 08 JUN 2001

S/N unknown

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: SORENSEN et al. Serial No.: unknown
Filed: concurrent herewith Docket No.: 12875.18USWO
Title: A METHOD AND AN APPARATUS FOR CUTTING OF TISSUE BLOCKS

CERTIFICATE UNDER 37 CFR 1.10

'Express Mail' mailing label number: EL669942107US

Date of Deposit: 8 June 2001

I hereby certify that this correspondence is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231.

By:

Name: Omesh Singh

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment, which is based on the Article 14 amendments, a copy of which is enclosed herewith:

IN THE ABSTRACT

Please insert the attached abstract page as the last page thereof.

IN THE CLAIMS

Please amend claims 3-5, 7, 10-20, 22-23, 27, 29-32, 34-35, and 37 as follows:

3. (Amended) A method according to claim 1, whereby the tissue block is positioned relative to the cutting members in a predetermined orientation corresponding to the orientation of tissue block in vivo.

4. (Amended) A method according to claim 1, whereby the tissue block is placed for cutting on a support surface and held in the predetermined position by applying a vacuum to one or more suction pads in the surface underneath the tissue block.

5. (Amended) A method according to claim 1, wherein the cutting members are mounted on a frame for engaging and sectioning the tissue block placed underneath the cutting members.

7. (Amended) A method according to claim 1, whereby the tissue block is centrally positioned on the support surface before the cutting action.

10. (Amended) An apparatus according to claim 8, wherein the distance between the cutting members can be adjusted.

11. (Amended) An apparatus according to claim 8, wherein the tension of the cutting members can be adjusted.

12. (Amended) An apparatus according to claim 8, wherein the cutting members are razor blades.

13. (Amended) An apparatus according to claim 8, wherein the cutting members are wires.

14. (Amended) An apparatus according to claim 1, wherein the support surface is provided with positioning means for allowing accurate positioning of a tissue block, preferably embedded in an embedding having predetermined reference surfaces.

15. (Amended) An apparatus according to claim 1, wherein the support surface is provided with vacuum supply means for retaining the tissue block in a predetermined position.

16. (Amended) An apparatus according to claim 14, wherein a centring means with a laser pointer are provided for accurate positioning of the tissue block on the support surface.

17. (Amended) An apparatus according to claim 14, wherein concentric centring marking circles are provided in the support surface and possibly supplemented with aiming crossing lines.

18. (Amended) An apparatus according to claim 14, wherein concentric recesses are provided in the support surface.

19. (Amended) An apparatus according to claim 14, wherein concentric circular suction rings are provided that can be supplied with vacuum from the vacuum supply means for retaining the tissue block.

20. (Amended) An apparatus according to claim 1, wherein the cutting members are connected to vibration means for vibration during the slicing action.

22. (Amended) An apparatus according to claim 21, wherein the vacuum in the vacuum supply means is generated by vacuum generating means connected to the pneumatic supply means.

23. (Amended) An apparatus according to claim 8, wherein the driving means comprise pillar guiding means provided on the support surface and linear actuation means for linear movement of the sectioning means towards the support surface along the path defined by the pillar guiding means.

27. (Amended) A method of preparing a tissue block for pathological examinations by encasing the tissue block in a tissue embedding in order to obtain a tissue block that is provided with reference positions for use in a method of cutting the tissue block according to claim 1 in an apparatus for cutting of a tissue block in slices with a predetermined orientation in the tissue block for obtaining a direct correlation of CT, MR or PET images for pathological examination, said apparatus comprising a support surface for receiving a tissue block, sectioning means comprising a multiple of cutting members, and driving means for moving the sectioning means towards the support surface for slicing a tissue block into sections said method comprising the steps of

filling a moulding form with an appropriate amount of non-toxic, biologically inert polymer moulding material, said form having at least one reference surface, and positioning a tissue block in said polymer moulding material in a predetermined position relative to said at least one reference surface, while the polymer moulding material is in its soft state.

29. (Amended) A method according to claim 27, whereby the tissue block is embedded in a bottom mould part and a top mould is formed in a top moulding form that is filled with polymer moulding material and placed on top of the lower moulding part with a partly encased tissue block, so that the tissue block is completely encased by the moulding.

30. (Amended) A method according to claim 27, whereby the tissue block is fixed to a reference moulding of predetermined dimensions and whereby said reference moulding is pivoted into a predetermined position in one or more directions, and then moulded into at least a bottom moulding.

31. (Amended) A method according to claim 27, whereby the polymer material is a cold polymerisate that polymerises by addition of water, such as a alginate plastic polymer.

32. (Amended) An apparatus for producing a tissue embedding according to a method according to claim 27 for use in an apparatus for cutting of a tissue block in slices with a predetermined orientation in the tissue block for obtaining a direct correlation of CT, MR or PET images for pathological examination, said apparatus comprising a support surface for receiving a tissue block, sectioning means comprising a multiple of cutting members, and driving means for moving the sectioning means towards the support surface for slicing a tissue block into sections, said apparatus comprising

first moulding means defining a reference moulding form for embedding a tissue block in a moulding, said first moulding means comprising an tubular side portion and first bottom plate means providing a bottom surface in the reference moulding form,

positioning means comprising at least one set of pivoting means for pivoting a reference mould, and

second moulding means for defining a bottom moulding form, said second moulding means comprising a retractable, tubular side wall and a second plate means for providing a bottom surface in the bottom moulding form.

34. (Amended) An apparatus according to claim 32, wherein a centrally disposed, retractable piston having a hemispherical end portion that extends into and forms part of the reference mould form when extended.

35. (Amended) An apparatus according to claim 32, wherein the pivoting means comprise two oppositely disposed, aligned pins that are provided in the outer edge region of the second moulding means and are radially insertable in the reference mould defining a pivot axis for pivoting the reference mould into a desired position.

37. (Amended) A tissue embedding for providing predetermined reference surfaces for accurate positioning of a tissue block in an apparatus for cutting of a tissue block in slices with a predetermined orientation in the tissue block for obtaining a direct correlation of CT, MR or PET images for pathological examination, said apparatus comprising a support surface for receiving a tissue block, sectioning means comprising a multiple of cutting members, and driving means for moving the sectioning means towards the support surface for slicing a tissue block into sections, for the performance of a method according to claim 1, whereby a tissue block, such as an internal organ, or another internal anatomical structure is at least partly fixed in a mould having a predetermined reference surface, preferably a bottom surface for accurate positioning in an apparatus for sectioning said tissue block for pathological examination purposes, said tissue embedding comprising mould parts made of a non-toxic plastic polymer material, in particular an alginate plastic polymer.

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 3-5, 7, 10-20, 22-23, 27, 29-32, 34-35, and 37.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Marked-up Copy".

A new abstract page is supplied to conform to that appearing on the publication page of the WIPO application, but the new Abstract page is typed on a separate page as required by U.S. practice.

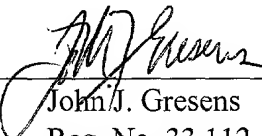
Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, John J. Gresens (Reg. No. 33,112), at (612) 371.5265.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Dated: 8 June 2001

By 
John J. Gresens
Reg. No. 33,112

JJG:hjh

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN**

I hereby declare that I am

- Check one ☐ a) () the owner of the small business concern identified below:
☒ b) (X) an official of the small business concern empowered to act on behalf of the concern identified below:

Insert company
name and
address

NAME OF CONCERN: HistOtech ApS

ADDRESS OF CONCERN: c/o Nestjyds Innovation A/S, Forskerparken,
Gustav Wieds Vej 10, DK-8000 Århus C,
Denmark

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled A method and an apparatus for cutting of tissue blocks by inventor(s) Jens Christian Hedemann Sørensen, Finn Geneser, Ulrik Kjørqaard Sørensen, * described in

- Check one, fill in if b) or c) ☐ a) () the specification filed herewith. Graziano Cancian and Carsten Reides Bjarkam
☐ b) () application serial no. _____, filed 8 June 2001
☐ c) () patent no. _____, issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c), if that person had made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). **NOTE:** Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

Insert co-owners, if any, and check a), b) or c) ☐ NAME _____
☐ ADDRESS _____
☐ a) () INDIVIDUAL b) () SMALL BUSINESS CONCERN c) () NONPROFIT ORGANIZATION

☐ NAME _____
☐ ADDRESS _____
☐ a) () INDIVIDUAL b) () SMALL BUSINESS CONCERN c) () NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereof, or any patent to which this verified statement is directed.

Insert ☐ NAME JENS CHRISTIAN HEDEMANN SØRENSEN
☐ TITLE MANAGING DIRECTOR
☐ ADDRESS SØTORFEN 43, 8250 EGAA, DENMARK
☐ SIGNATURE [Signature] DATE June 6th, 2001

Sign, date

A METHOD AND AN APPARATUS FOR CUTTING OF TISSUE BLOCKS

The present invention relates to a method and an apparatus for cutting of a tissue block for pathological examination. The invention further relates to a method an apparatus for preparing a tissue block for sectioning in such an apparatus by use of
5 such method. The invention also relates to a tissue embedding obtained by said method and apparatus for preparing a tissue block.

The cutting of larger tissue blocks for pathological examination has normally been
10 performed by hand. This technique involves a special pathology knife that is used for cutting slices of parenchymateous organs such as brain, liver, kidney and heart. This cutting technique is quick and sufficient for the daily qualitative examinations on a pathological institute. The technique, however, result in tissue sections with highly variable form and thickness, just as the hand cutting does not prevent deformation of
15 the organ.

From US 5,148,729 a biological tissue slicer is known that can produce thin slices of live tissue for biochemical, pharmacological or toxicological studies. With this machine a thin slice of tissue can be peeled off the tissue block one at the time by a
20 reciprocally cutting blade. The slices obtained hereby are completely inadequate for pathological examination purposes.

US 4,820,504 discloses a method of preparing a multi-specimen tissue block and sections thereof, where a plurality of different anitigenically reactive tissue
25 specimens are formed into a rods and embedded in a medium and then sliced off into sections which each contain a cross-section of the rod. With this technique, the resulting tissue slices are inaccurate in form due to possible deformation during the formation and during the slicing of a rod. Moreover, these sections are only usable as check samples of the different tissues in the multi-specimen tissue block from which
30 the section is sliced off.

CONFIRMATION COPY

The present techniques for preparing tissue sections for pathological examination are in accurate and does prevent deformation of the tissue block to an acceptable degree.

It is the object by the present invention to circumvent the problems that lead to bias when quantitative organ or tissue examinations are desired. Another object of the invention is to provide for new quantitative unbiased stereological techniques which require cutting of the tissue in question in sections with equal thickness and orientation.

- 10 These objects are achieved by a method for cutting of a tissue block in slices with a predetermined orientation in the tissue block preferably corresponding to orientation of the plane of a scanning, such as a CT, MR or PET scanning, wherein the tissue block, such as an internal organ or other internal anatomical structures, is placed with a predetermined position and then simultaneously sliced into a multiple of sections.
- 15 In a second aspect, the invention involves an apparatus for cutting of a tissue block in slices with a predetermined orientation in the tissue block for obtaining a direct correlation of CT, MR or PET images for pathological examination, said apparatus comprising a support surface for receiving a tissue block, sectioning means comprising a multiple of cutting members, and driving means for moving the
- 20 sectioning means towards the support surface for slicing a tissue block into sections.

- The invention circumvents the problems that lead to bias when quantitative organ or tissue examinations are desired. The invention is ideally suited for the new quantitative unbiased stereological techniques which require cutting of a tissue block
- 25 in sections with equal thickness and orientation. The invention also allows the resulting organ or tissue sections to be directly correlated to corresponding scanning planes from imaging modalities such as e.g. computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).

- 30 In a third and fourth aspects, the invention involves a method and an apparatus for preparing a tissue block for sectioning in the slicing machine. By this preparation, the organ or tissue is embedded in an alginate plastic polymer mould that together with

the embedded tissue subsequently can be sectioned in the tissue slicing machine. finally the invention also involves a tissue embedding prepared by the use of such method.

- 5 In a first embodiment of the method and apparatus for cutting of tissue blocks invention, the sectioning means comprise a multiple of parallel cutting members arranged in a cutting frame. Hereby, the sections obtained by the simultaneous sectioning of the tissue block can be easily produced by lowering a frame with cutting members down to and through the underlying tissue block.

10

In a preferred embodiment the distance between the cutting members can be adjusted. Hereby sections of a predetermined thickness can be obtained.

- 15 The tension of the cutting members can preferably also be adjusted. Hereby, the risk of causing a deformation of the tissue during the cutting action.

In a first embodiment the cutting members are razor blades. This ensures a sharp and accurate cut without deforming the tissue block during the slicing.

- 20 In an alternative embodiment the cutting members can be wires. Hereby, a more simple and less expensive solution can be provided where appropriate.

- 25 In the preferred embodiment of the invention, the support surface is provided with positioning means for allowing accurate positioning of a tissue block, preferably embedded in an embedding having predetermined reference surfaces. This ensures that the tissue can be positioned relative to the cutting members in such a way that the resulting sections correspond to scanning planes used in a scanning.

- 30 In the preferred embodiment, the support surface is provided with vacuum supply means for retaining the tissue block in a predetermined position. Hereby, a simple and hygienic and stable retention means is provided.

In the preferred embodiment centring means with a laser pointer are provided for accurate positioning of the tissue block on the support surface. The laser can be used for accurate position of the tissue block relative to the cutting members by assisting the positioning of the tissue block in the centre of the support surface.

5

This positioning could also comprise concentric centring marking circles in the support surface and possibly supplemented with an aiming crossing lines. This could e.g. be in the form of concentric recesses in the support surface.

10 In particular, concentric circular suction rings are provided that can be supplied with vacuum from the vacuum supply means for retaining the tissue block. This is particularly advantageous since the vacuum can be used not only for the retention but also for the aligning or centring of the tissue block.

15 The cutting members are preferably connected to vibration means for vibration during the slicing action, in order to facilitate the cutting action and prevent deformation of the tissue during the cutting action.

20 The vibration means could advantageously comprise a pneumatic vibrator that is connected to pneumatic supply means.

The vacuum in the vacuum supply means could preferably be generated by vacuum generating means connected to the pneumatic supply means. Hereby, only the number of control or supply systems needed can be reduced.

25

In a preferred embodiment, the driving means comprise pillar guiding means provided on the support surface and linear actuation means for linear movement of the sectioning means towards the support surface along the path defined by the pillar guiding means. This allows an accurate and smooth linear movement of the cutting
30 frame up and down relative to the support surface for cutting the tissue. By the use of a die set for the guiding means, the travel of the cutting frame can be carried out virtually without slack whereby an accuracy in the sectioning is achieved. The linear

actuation means preferably comprise a threaded driving spindle parallel to the guide means and a corresponding threading in the cutting frame.

In a first embodiment, the threaded driving spindle is provided with a handle for manual operation. This offers a simple apparatus for carrying out the sectioning. However, in an alternative embodiment, the driving spindle can be pneumatically or electrically driven.

In order to ensure a good positioning of the tissue block in the apparatus and to prevent deformation during the cutting, the invention also relates to method and an apparatus for preparing a tissue block. This method comprises the steps of filling a moulding form with an appropriate amount of non-toxic, biologically inert polymer moulding material, said form having at least one reference surface, and positioning a tissue block in said polymer moulding material in a predetermined position relative to said at least one reference surface, while the polymer moulding material is in its soft state.

By this method, the tissue block is provided with regular outer surfaces that due to the form of the mould can adapted to the support surface of the sectioning apparatus.

The tissue block is in a preferred embodiment positioned in the polymer material with an orientation that corresponds to the orientation of the tissue block in vivo. Hereby, a correlation between scanning images and the sections can be ensured.

The tissue block is embedded in a bottom mould part and a top mould is formed in a top moulding form that is filled with polymer moulding material and placed on the top of the lower moulding part with a partly encased tissue block, so that the tissue block is completely encased by in the moulding. This provides an effective insurance against the otherwise free top part of the tissue to be deformed by the cutting members.

The tissue block is in a preferred method of preparation fixed to a reference moulding of predetermined dimensioned and that said reference moulding is pivoted into a predetermined position in one or more directions, and then moulded into at least a bottom moulding. Hereby, the orientation of the tissue block can be vary accurately embedded relative to the reference surfaces.

The polymer material that is preferably used, is a cold polymerisate that polymerises by addition of water, such as an algino plastic polymer.

10 The apparatus and the details of the functions of the apparatus can be appreciated in the dependent claims 33 to 36.

Finally, the invention also relates to a tissue embedding comprising a tissue block made by this preparation method and apparatus. This tissue embedding providing the tissue block with regular reference surfaces ensures an accurate cutting of slices of the block for pathological and other purposes. It is realised that this technique of embedding the tissue block in an alginate or similar suitable moulding material can advantageously be used prior to any cutting action, whether a slice at the time is cut or - as it is the case in the first aspect of the invention - that the slices are cut simultaneously.

The invention will be described more detailed below with reference to the accompanying drawings, in which

- 25 Fig. 1 is a perspective view of an apparatus for sectioning a tissue block according to the invention,
fig. 2 shows a cutting frame of said apparatus,
fig. 3a and 3b show the tissue block embedded in an alginate bottom and with an alginate top mould,
30 fig. 4a to 4g show the embedding apparatus and the steps in the oriented alginate embedding procedure, and
fig. 5 is a top view of the embedding apparatus of figs. 4a-4g.

Referring to fig. 1, a preferred embodiment of the tissue slicing machine is shown. The tissue slicing machine stand on an aluminium or steel base plate 1 that preferably rest on a rubber pad or rubber knobs attached to the base plate 1. The base plate 1 is connected to the aluminium or steel top plate 2 by pillar guiding means comprising two the pillars 3 which through operation of the crank and spindle 8, 9 allow lowering and elevation of the top plate 2 in relation to the base plate 1. In the centre of the top plate 2 a rectangular hole leaves room for attachment of the cutting frame 12. The cutting frame 12 is fixed in place by screws or a handle on the side of the cutting frame 12. The cutting frame 12 comprises a number of cutting members 14 (see fig. 2), preferably in the form of thin razor blades of hardened steel. The razor blades 14 are spaced by spacing blocks 38 that can be made of metal or plastic. In the preferred embodiment the cutting frame 12 is exchangeable as a whole when the razor blades 12 are worn out and has lost their sharpness. In another embodiment the knife frame 12 allow changing or removal of individual blades 14, just as spacing blocks 38 of different thickness can be used. On the side of the top plate 2 a pneumatic or electric operated vibrator 4 is placed. It will when activated set the sectioning means comprising the top plate 2 and knife frame 12 into vibrations along the long axis of the razor blades 14. This facilitates the cutting procedure by lowering of the friction as the knives 14 pass through the tissue 20 and alginate block 25 (see figs. 3a and 3b). On the side of the top plate 2 there is also placed a pneumatic valve 7 for pressurised air to operate the embodiment with the pneumatic vibrator 4. The pneumatic vibrator 4 is connected to the pneumatic air valve 7 through a pneumatic hose 5. The pneumatic air valve 7 is connected to a pressurised air source at the pneumatic intake 6. On the other side of the top plate 2 or on the base plate 1 in another embodiment a valve 13 for vacuum with vacuum outtake 10 is placed. In one embodiment the vacuum outtake 10 is connected to a vacuum pump (not shown). In a second embodiment the vacuum is produced by a second pneumatic air flow valve (not shown). The vacuum hose 15 connects the vacuum valve 13 to a recess and associated apertures 16 for retention and vacuum fixation of alginate and tissue block 25. In the support surface of the base plate 1 concentric circles 17 and a cross hair cut allow centring of alginate and tissue block 25. To further aid the centring of the

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tissue and alginate block 25 a laser pointer 11, that point to the central vacuum hole of the vacuum apertures 16, is provided on the top plate.

Fig. 2 show an embodiment of the cutting frame 12 consisting of knives 14 that are angled in relation to the horizontal plane of the base plate 1. This embodiment will reduce friction and deformation during the cutting of the tissue alginate block 25. In one embodiment the knife frame 12 consist of razor blades 14 that cannot be replaced, and the whole frame 12 must be changed when the blades become dull. In another embodiment the knife frame allow exchanging of individual blades and use of spacing blocks 38 with different thickness.

The bearing construction of the tissue slicing machine comprises a pillar guided base and top plate 1 and 2. The top plate 2 contains a set of parallel oriented knives 14 positioned in a frame 12. The knives 14 are mounted in a "knife frame set" and the distance between the knives 14 are spaced by high tolerance spacing blocks 38 with an equal thickness. Changing between different knife frame sets can vary the knives distance. The frame of the tissue slicing machine is equipped with a pneumatic vibrator 4 that make the knife frame set vibrate along its longitudinal axis, i.e. along the cutting edge of the knives. The vibration 4 of the knife frame 12 diminishes friction as it moves through alginate and tissue block 25. The knife frame with vibrator is mounted on a columnar lead equipped with a crank 19 that by turning allow movement of the knife frame 12 in the vertical plane. For fixation of alginate and tissue block 25 the base plate 1 of the tissue slicing machine is equipped with a suction pad that is activated by opening a vacuum valve after placement of the alginate tissue block. The concentric rings of the suction pad also serve to centre the alginate tissue block, just as a laser pointer identifies the centre.

Referring to figure 3a and 3b, any tissue block 20 or organ can be embedded into an alginate plastic mould 25. In one embodiment of this invention the tissue 20 is first embedded in an alginate bottom mould 22. This can be done by pouring the mixture of alginate powder and water in to a moulding form 21, such as a plastic jar, followed by placement of the tissue 20 into the still soft alginate-water mixture in the

mould 22. When the alginate bottom 22 has hardened an alginate top mould 23 can be cast in a similar fashion by placing a second moulding form 24, such as a second plastic jar 24. This top mould 23 can subsequently be removed for better placement of the alginate bottom 22 in the tissue slicing machine as shown in fig. 1 by then use
5 of anatomical landmarks. In a second embodiment the tissue 20 can be cast entirely into alginate followed by CT or MRI scanning of the tissue and alginate block. When placed in the tissue slicing machine in same way as in the CT or MRI scanner the resulting tissue sections will correspond to the scanning planes. In a third embodiment of the embedding procedure, alginate embedded tissue can be cut on
10 prior art tissue sectioning machines, such as cryostats, vibratomes and microtomes.

For tissue embedding alginate plastic polymer from Bayer Dental was used. The alginate is a non-toxic cold polymerisate that polymerises after addition of water. The alginate powder is stirred into the water and then poured into a plastic jar or
15 other moulding form 21 of appropriate size for the tissue block in question. The organ or tissue block 20, such as a pig brain, is then placed in the still soft polymer and hold in place until the alginate hardens. The embedding is the crucial step in the process and care must be taken to orient the tissue 20 in the alginate as it is oriented in vivo. For less accuracy this can achieved by the use of an angle protractor 34-36
20 and anatomical landmarks on the tissue 20 in question. For high accuracy the tissue embedder must be used. A further option is to cast another alginate mould 24 on top of the tissue and alginate bottom 22. This done in order to support the tissue 20 during the cutting procedure and avoid tissue deformation. In the following this will be described as a tissue and alginate bottom 22 and an alginate lid 24.

25 An alternative strategy that can be used, if no scanning is needed before pathological extraction of the organ, is to embed the organ 20 in alginate and then perform the desired computer assisted scanning modality on tissue and alginate block 25 followed by the sectioning as described by the first aspects of the present invention.
30 This strategy abolishes the need for orientation of the tissue block 20 as the resulting digital image scanning planes will correspond to the histological sections provided

that the tissue and alginate block 25 is placed in the cutting machine in the same fashion as in the CT, MRI or PET scanner.

In the apparatus for cutting of tissue blocks, the tissue block 25 with the embedded tissue 20, is placed on the suction pads 16 of the support surface and centred in relation to the cutting frame 12 by use of the concentric circles 17 of the tissue slicing machine base plate 1 and the laser pointer 11. Following the centring the alginate tissue block 25 is fixed by activation of the vacuum valve 13 and is now ready for the cutting. This can be done with or without the alginate lid 24. An opening of the pneumatic valve 7 activates the pneumatic vibrator 4 and the cutting frame 12 starts vibrating. By a steady rotating movement, the crank 19 of the columnar lead is turned and the cutting frame 12 is lowered through the alginate and tissue block 25. The cutting results in a set of alginate and tissue slabs (not shown) that are of equal thickness and oriented corresponding to the scanning plane of the given computerised scanning modality.

Referring to figures 4a to 4g a method and an apparatus for preparing a tissue block 20 by embedding the tissue block 20 in alginate plastic polymer. This can be done in such a way that the tissue 20 is oriented to existing CT, MRI or PET scanning planes.

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Fig. 4a shows the embedding apparatus that comprises of a central plastic rod 28 with a spheric top end 28a and two concentric plastic cylinders, i.e. an inner cylinder 29 and an outer cylinder 30. The rod 28 is fixed to a plastic base plate 31, where upon also the cylinders 29, 30 rest in their retracted positions. On top of the outer cylinder 30 four plastic pins 33 with or without a screw thread are placed at 90 degrees interval and orthogonal to the long axis of the cylinder 30 (see fig. 5).

25

A reference moulding form 27 is placed on plate means 32 comprising two half parts placed on the inner cylinder 29 on each side of the rod 28. Hereby, a reference moulding form is defined. This form is filled with polymer moulding material 26 in which the tissue block 20 is placed. This means that the tissue block 20 is embedded

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in a reference mould 26, such as shown in fig. 4b, where the plate means 32 and the form 27 is removed.

Fig. 4c shows a tissue and alginate reference mould 26 placed in the embedding apparatus. The alginate mould 26 is first fixed with two plastic pins 33 facing each other at 180 degrees. This plane can be defined as the X plane. The tilt angle of the tissue and alginate reference mould 26 in relation to the horizontal Z plane, as determined from the desired CT, MRI or PET scanning, is determined by an angle protractor 36 (see fig. 4d) in one embodiment. In a second embodiment the angle protractor 36 is equipped with a laser guide 34 directing a beam 35 at the mould for a measure of the angle of inclination. When the tissue and alginate reference mould 26 is fixed in the desired angle in the X plane, it is then fixed in a similar way by the two plastic pins 33 placed orthogonally in the Y plane.

Fig. 4e shows the casting of the second alginate bottom 22. The shape of the bottom mould 22 is adapted to fit into the tissue slicing machine of fig. 1. First, the outer cylinder 30 is raised and a second base plate 37 is slid into a corresponding horizontal opening in the outer plastic cylinder 30, followed by casting of the second alginate bottom 22, as the outer cylinder 30 forms the side part of the moulding form.

Fig. 4f shows the placement of a top form 21 on the outer cylinder 30 followed by casting of an alginate top mould 24 on the top of the bottom mould 22 and the tissue block 20.

Fig. 4g shows the embedded tissue block 20 with its alginate moulding 25 - i.e. the reference mould 26, bottom mould 22 and top mould 24 - free of the embedding apparatus after the outer cylinder 30 has been slid back towards the base plate 31.

Fig. 5 shows a top view of the outer cylinder 30, inner cylinder 29, centre rod 28 and plastic pins 33 for pivoting the reference mould 26 of the tissue block.

This embedding apparatus allows accurate three dimensional orientation of a tissue reference moulding 26 in relation to CT, MRI or PET scans. Following the accurate orientation of the tissue reference moulding 26, a second moulding is performed to produce a second alginate bottom 22 with an outer surface that will fit into the tissue slicing machine. If desired a final alginate lid 24 can be cast on top of the tissue 20 and alginate bottom 22 in order to avoid tissue deformations during the cutting procedure. The embedding apparatus comprises a circular rod 29 of transparent plastic, such as plexi-glass or similar material, two outer concentric plastic cylinders 29 and 30, fixation pins 33, semicircular plastic plates 32 and an insertable base plate 37 that preferably also is made from a plastic material.

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REVISED PATENT CLAIMS:

1. A method of cutting of a tissue block of an internal organ or other internal anatomical structures into slices having a predetermined orientation in the tissue block corresponding to an orientation of a plane of a preceding scanning, such as a CT, MR or PET scanning, wherein the tissue block is placed in a predetermined position with respect to a multiple of cutting members and then simultaneously sliced into a multiple of sections.
2. A method according to claim 1, whereby the simultaneous sectioning is performed by a multiple of cutting members oriented in parallel.
3. A method according to claim 1 or 2, whereby the tissue block is positioned relative to the cutting members in a predetermined orientation corresponding to the orientation of tissue block in vivo.
4. A method according to any of the previous claims, whereby the tissue block is placed for cutting on a support surface and held in the predetermined position by applying a vacuum to one or more suction pads in the surface underneath the tissue block.
5. A method according to claim 1 to 4, wherein the cutting members are mounted on a frame for engaging and sectioning the tissue block placed underneath the cutting members.
6. A method according to claim 5, whereby the cutting members are vibrated during the cutting action.
7. A method according to any of the previous claims, whereby the tissue block is centrally positioned on the support surface before the cutting action.

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8. An apparatus for cutting of a tissue block in slices with a predetermined orientation in the tissue block for obtaining a direct correlation of CT, MR or PET images for pathological examination, said apparatus comprising
- 5 a support surface for receiving a tissue block,
- sectioning means comprising a multiple of cutting members, and
- driving means for moving the sectioning means towards the support surface for
- 10 slicing a tissue block into sections.
9. An apparatus according to claim 8, wherein the sectioning means comprise a multiple of parallel cutting members arranged in a cutting frame.
- 15 10. An apparatus according to claim 8 or 9, wherein the distance between the cutting members can be adjusted.
11. An apparatus according to any of the claims 8 to 10, wherein the tension of the cutting members can be adjusted.
- 20 12. An apparatus according to any of the claims 8 to 11, wherein the cutting members are razor blades.
13. An apparatus according to any of the claims 8 to 11, wherein the cutting
- 25 members are wires.
14. An apparatus according to any of the previous claims, wherein the support surface is provided with positioning means for allowing accurate positioning of a tissue block, preferably embedded in an embedding having predetermined reference
- 30 surfaces.

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15. An apparatus according to any of the previous claims, wherein the support surface is provided with vacuum supply means for retaining the tissue block in a predetermined position.
- 5 16. An apparatus according to claim 14 or 15, wherein a centring means with a laser pointer are provided for accurate positioning of the tissue block on the support surface.
- 10 17. An apparatus according to the claims 14 to 16, wherein concentric centring marking circles are provided in the support surface and possibly supplemented with aiming crossing lines.
18. An apparatus according to the claims 14 to 16, wherein concentric recesses are provided in the support surface.
- 15 19. An apparatus according to any of the claims 14 to 18, wherein concentric circular suction rings are provided that can be supplied with vacuum from the vacuum supply means for retaining the tissue block.
- 20 20. An apparatus according to any of the previous claims, wherein the cutting members are connected to vibration means for vibration during the slicing action.
21. An apparatus according to claim 20, wherein the vibration means comprise a pneumatic vibrator that is connected to pneumatic supply means.
- 25 22. An apparatus according to claim 21 and any of the claims 14 to 19, wherein the vacuum in the vacuum supply means is generated by vacuum generating means connected to the pneumatic supply means.
- 30 23. An apparatus according to any of the claims 8 to 22, wherein the driving means comprise pillar guiding means provided on the support surface and linear actuation

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means for linear movement of the sectioning means towards the support surface along the path defined by the pillar guiding means.

24. An apparatus according to claim 23, wherein the linear actuation means comprise
5 a threaded driving spindle parallel to the pillar guide means and a corresponding threading in the cutting frame.

25. An apparatus according to claim 24, wherein the threaded driving spindle is provided with a handle for manual operation.

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26. An apparatus according to claim 23, wherein the driving spindle is pneumatically, hydraulically or electrically driven.

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27. A method of preparing a tissue block for pathological examinations by encasing the tissue block in a tissue embedding in order to obtain a tissue block that is provided with reference positions for use in a method of cutting the tissue block according to any of claims 1 to 7 in an apparatus according to any of claims 8 to 26, said method comprising the steps of

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filling a moulding form with an appropriate amount of non-toxic, biologically inert polymer moulding material, said form having at least one reference surface, and positioning a tissue block in said polymer moulding material in a predetermined position relative to said at least one reference surface, while the polymer moulding material is in its soft state.

25

28. A method according to claim 27, whereby the tissue block is positioned in the polymer material with an orientation that corresponds to the orientation of the tissue block in vivo.

30

29. A method according to claim 27 or 28, whereby the tissue block is embedded in a bottom mould part and a top mould is formed in a top moulding form that is filled with polymer moulding material and placed on top of the lower moulding part with a

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partly encased tissue block, so that the tissue block is completely encased by the moulding.

30. A method according to any of the claims 27 to 29, whereby the tissue block is
5 fixed to a reference moulding of predetermined dimensions and whereby said reference moulding is pivoted into a predetermined position in one or more directions, and then moulded into at least a bottom moulding.

31. A method according to any of the claims 27 to 30, whereby the polymer material
10 is a cold polymerisate that polymerises by addition of water, such as a alginate plastic polymer.

32. An apparatus for producing a tissue embedding according to a method according to any of the claims 27 to 30 for use in an apparatus according to any of the claims 8
15 to 26, said apparatus comprising

first moulding means defining a reference moulding form for embedding a tissue block in a moulding, said first moulding means comprising an tubular side portion and first bottom plate means providing a bottom surface in the reference moulding
20 form,

positioning means comprising at least one set of pivoting means for pivoting a reference mould, and

25 second moulding means for defining a bottom moulding form, said second moulding means comprising a retractable, tubular side wall and a second plate means for providing a bottom surface in the bottom moulding form.

33. An apparatus according to claim 32, wherein third moulding means are provided
30 for defining a top moulding form, said third moulding means comprising a tubular side wall form with a cross section generally corresponding to the tubular side wall of the second moulding means.

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34. An apparatus according to claim 32 or 33, wherein a centrally disposed, retractable piston having a hemispherical end portion that extends into and forms part of the reference mould form when extended.

5

35. An apparatus according to any of the claims 32 to 34, wherein the pivoting means comprise two oppositely disposed, aligned pins that are provided in the outer edge region of the second moulding means and are radially insertable in the reference mould defining a pivot axis for pivoting the reference mould into a desired position.

10

36. An apparatus according to claim 35, wherein two sets of pivoting means are provided defining two preferably mutually orthogonal pivot axes.

15

37. A tissue embedding for providing predetermined reference surfaces for accurate positioning of a tissue block in an apparatus according to any of the claims 8 to 26 for the performance of a method according to any of the claims 1 to 7, whereby a tissue block, such as an internal organ, or another internal anatomical structure is at least partly fixed in a mould having a predetermined reference surface, preferably a bottom surface for accurate positioning in an apparatus for sectioning said tissue block for pathological examination purposes, said tissue embedding comprising mould parts made of a non-toxic plastic polymer material, in particular an alginate plastic polymer.

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38. A tissue embedding according to claim 37, wherein the tissue block is provided with a bottom mould part and a top mould part encasing the tissue block inside said mould parts.

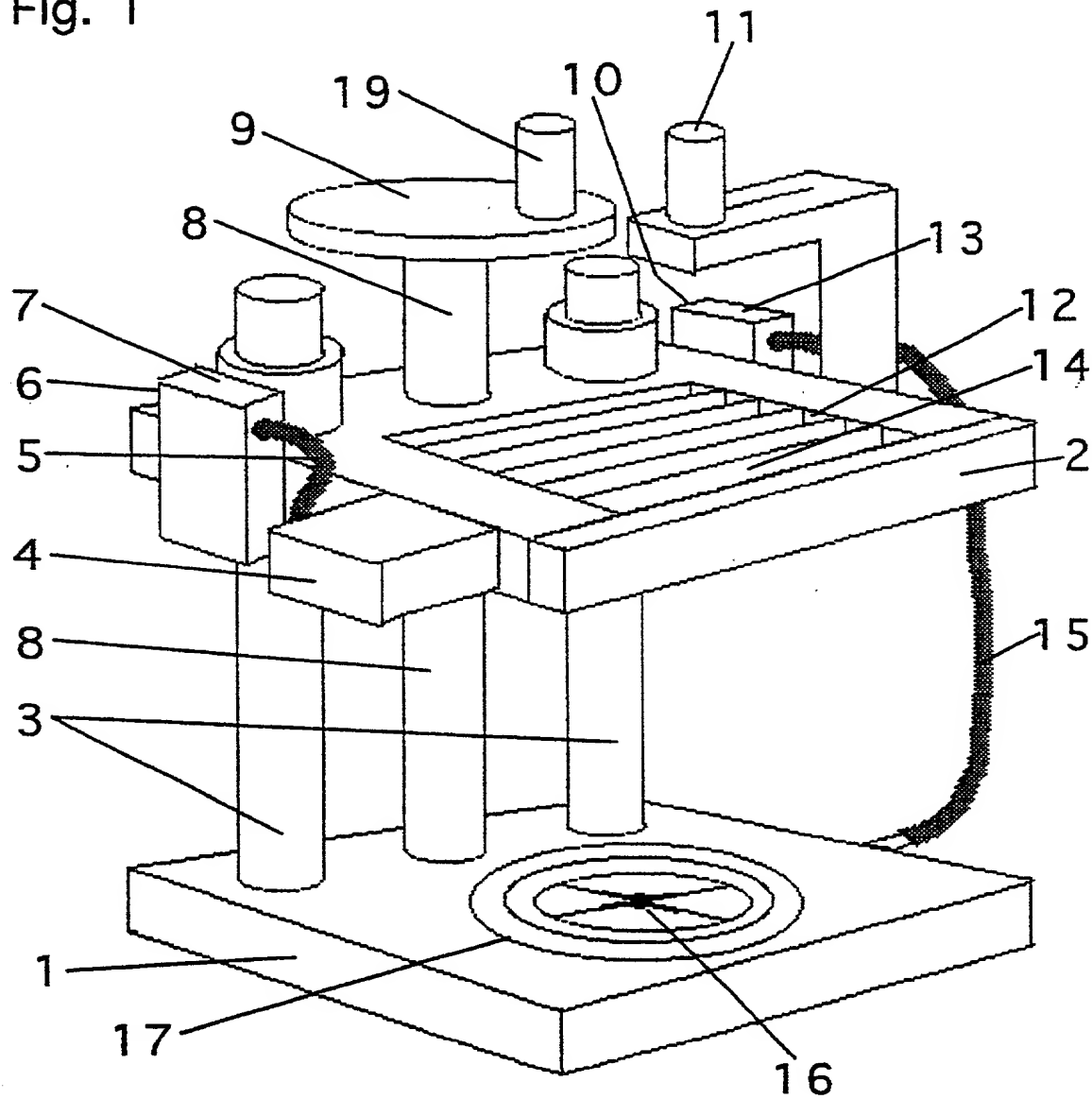
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39. A method of placing a reference grid on a section of a tissue block from an apparatus according to claim 8, whereby said reference grid allows a direct correlation of one or more tissue volumes to corresponding digital imaging volumes from CT, MR or PET imaging modalities.

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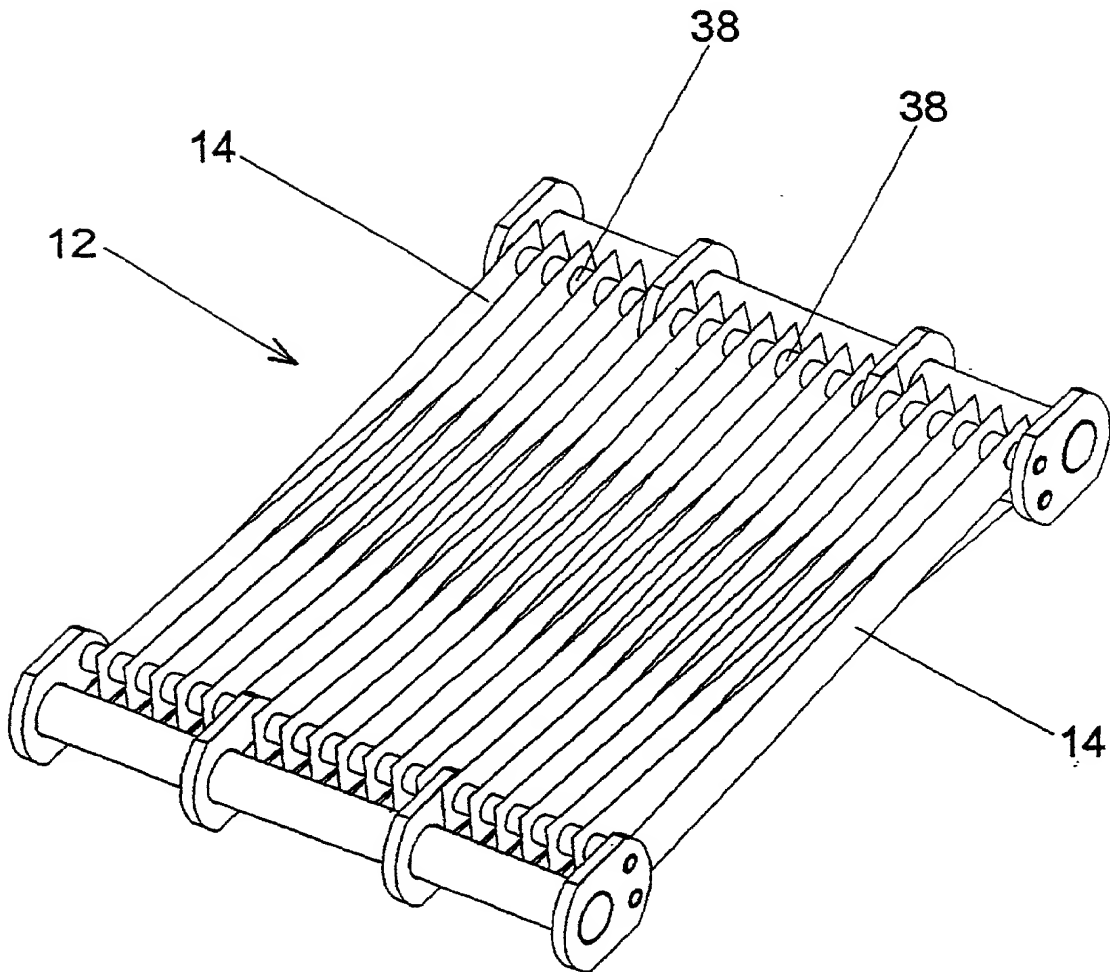
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Fig. 1



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Fig. 2



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Fig. 3a

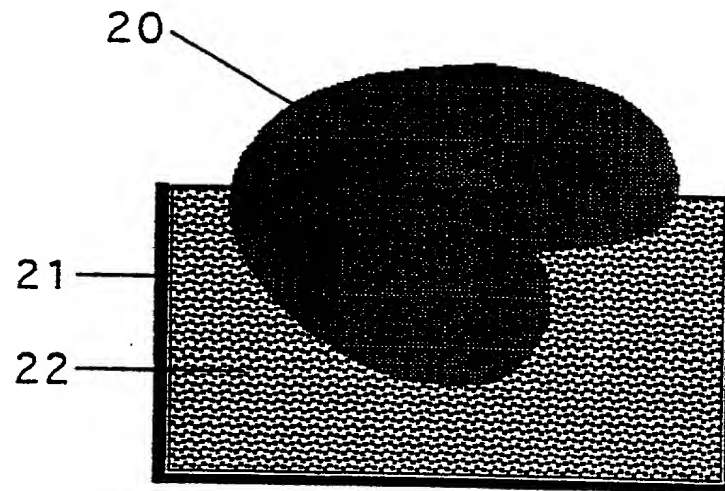
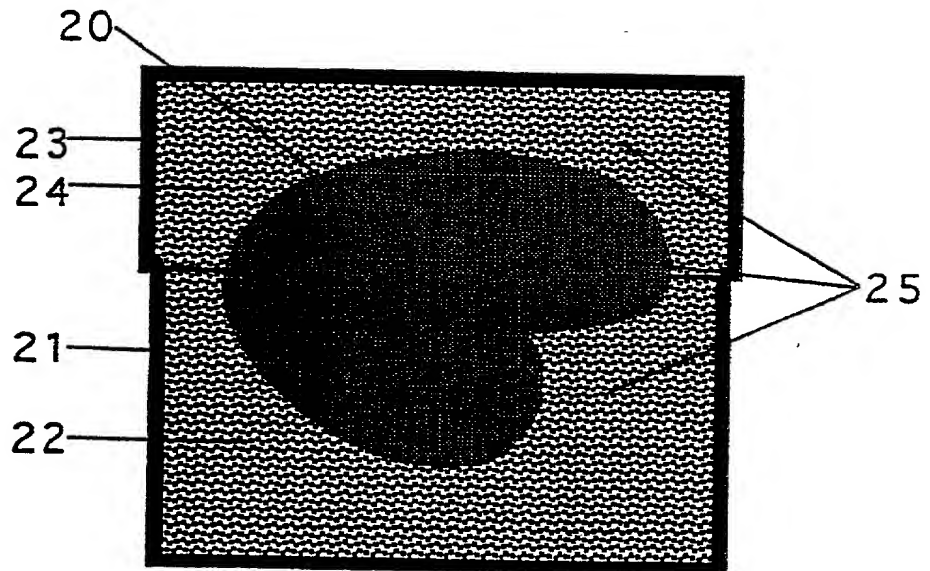
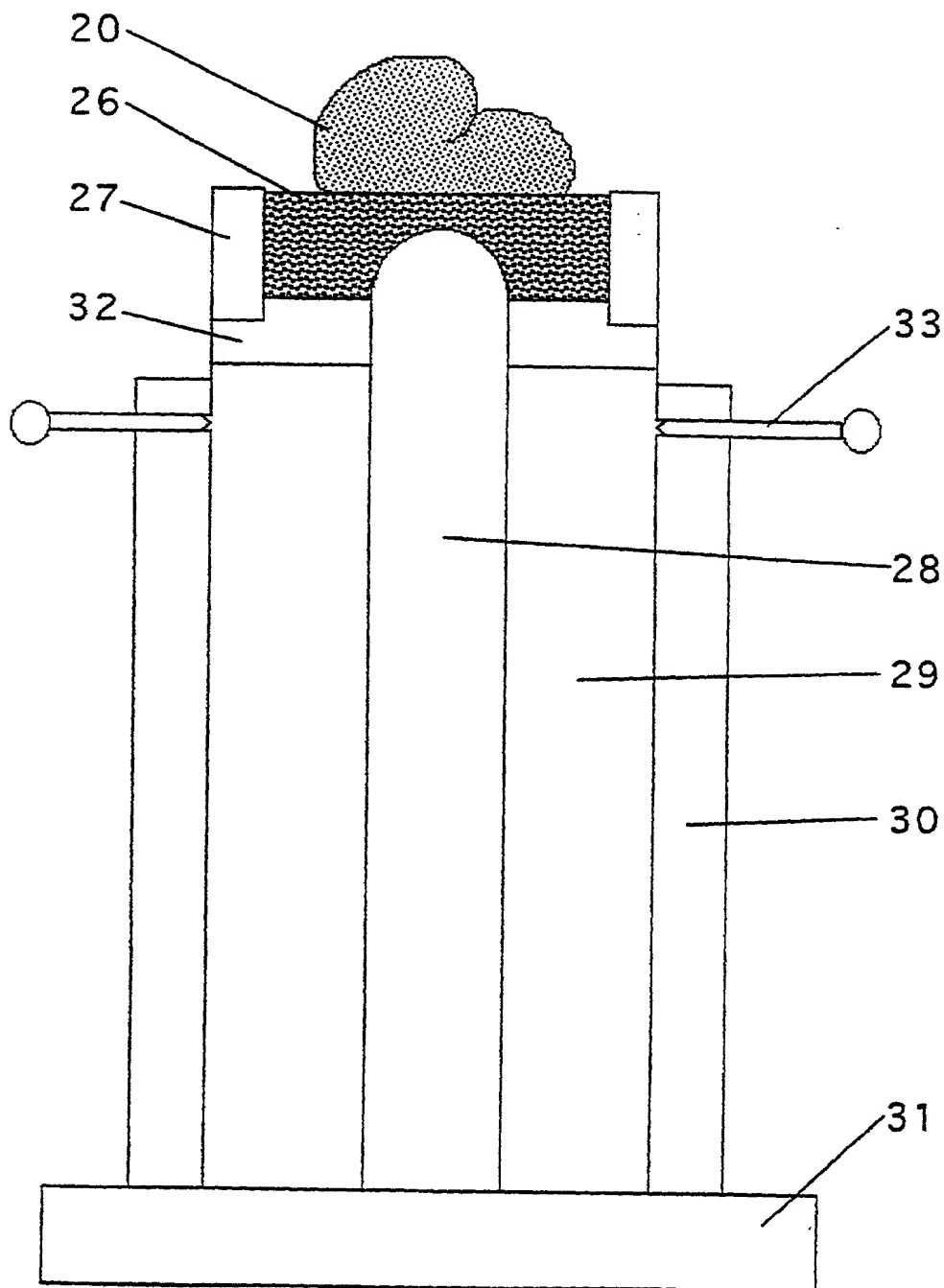


Fig. 3b



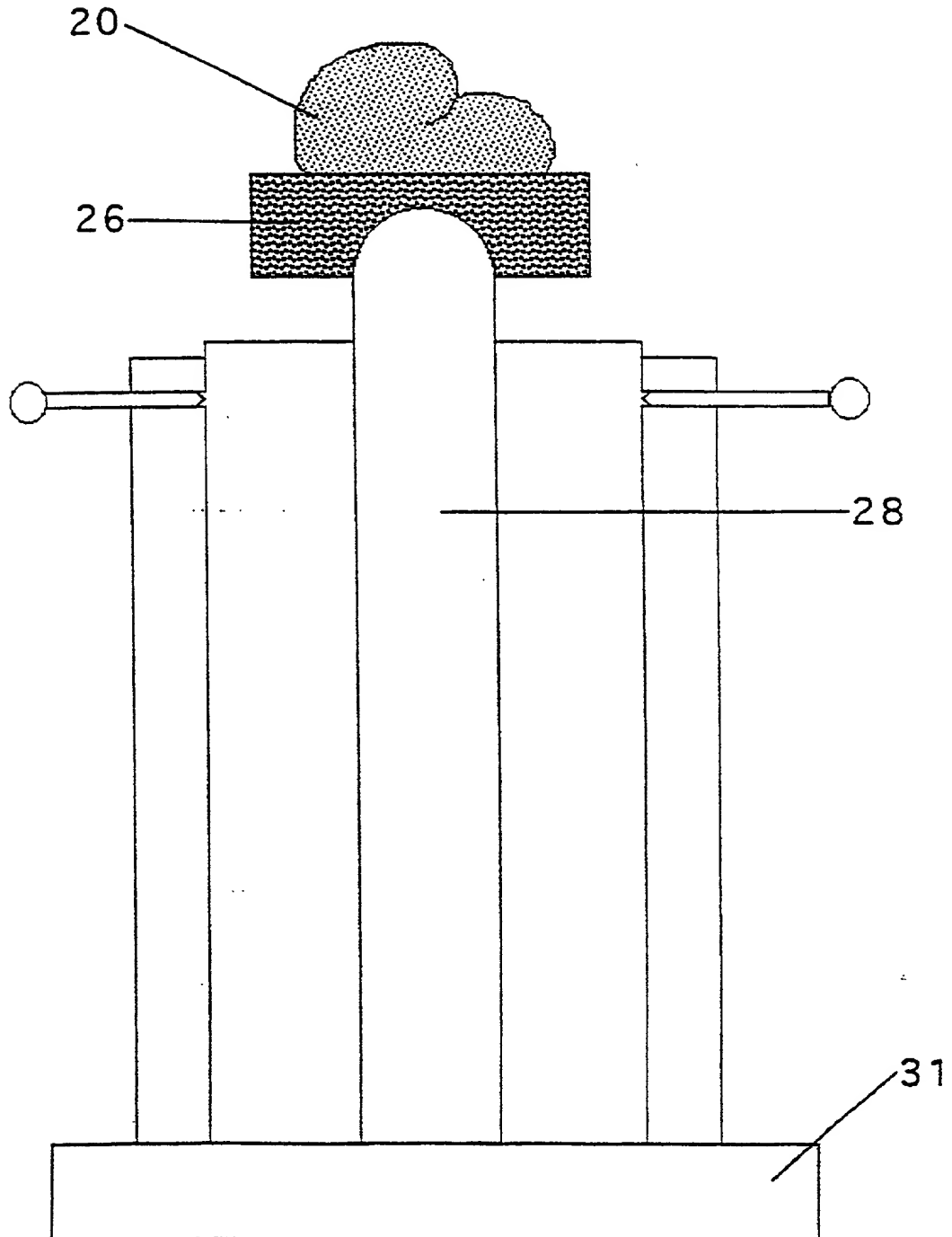
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Fig. 4a



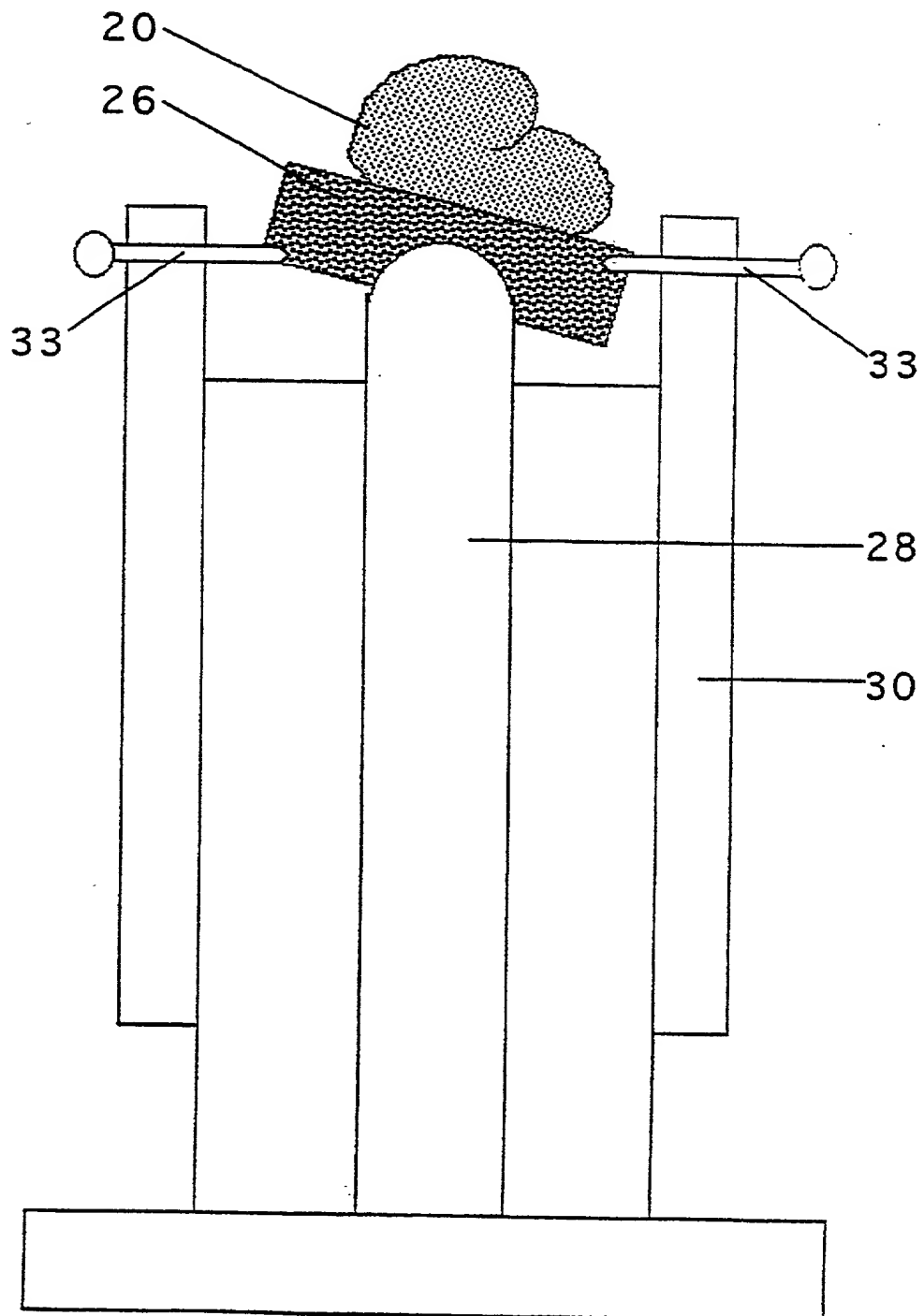
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Fig. 4b



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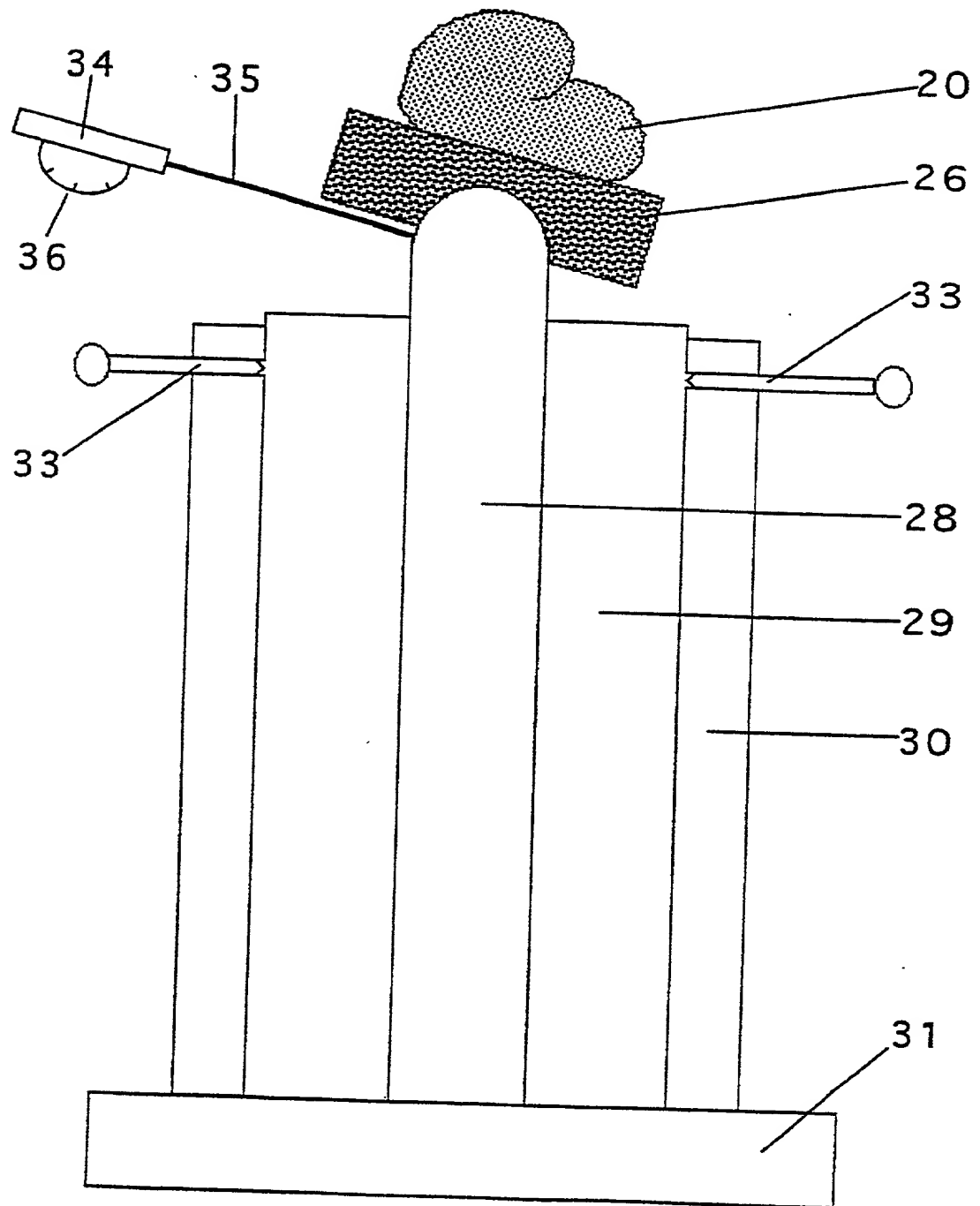
Fig. 4c



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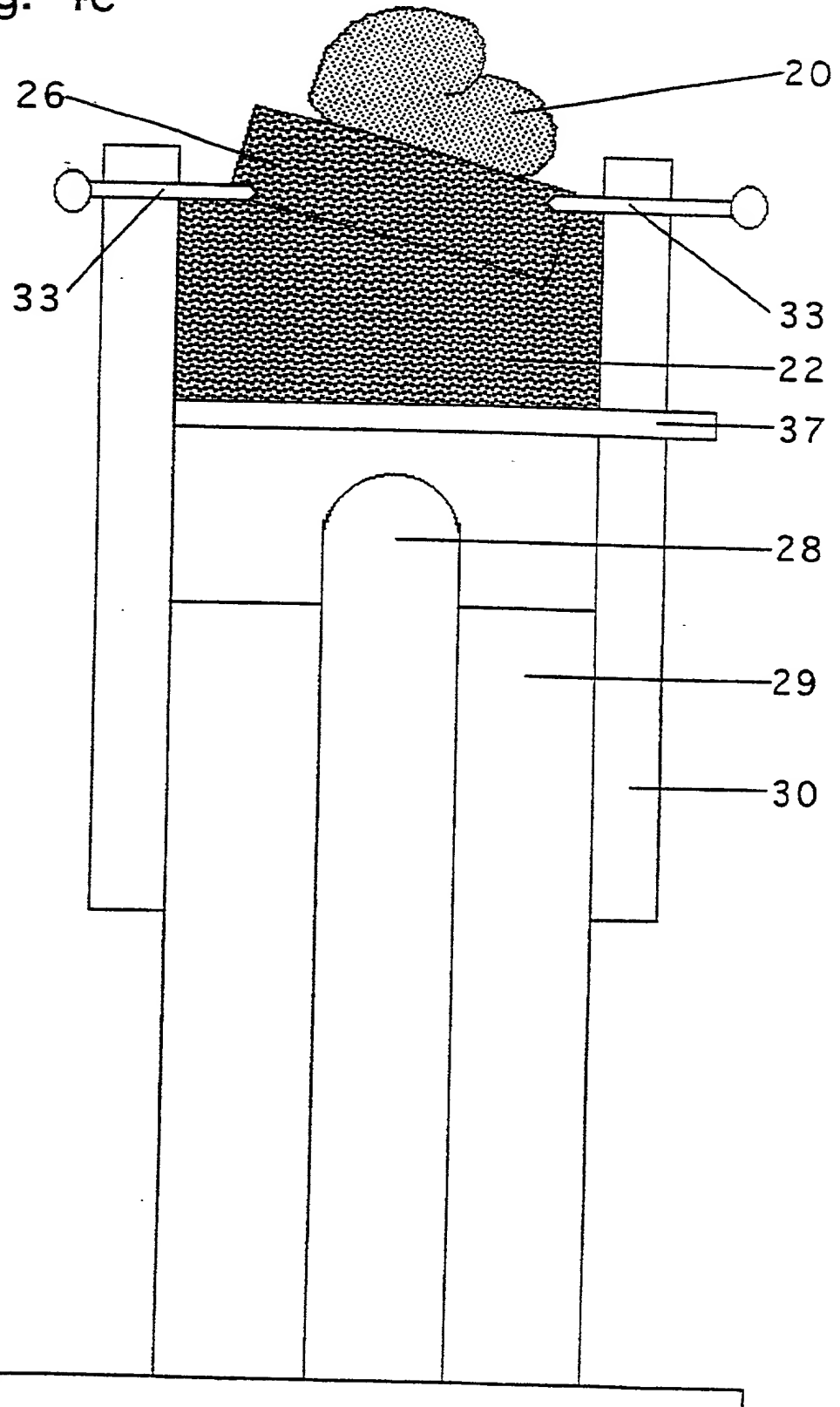
Fig. 4d



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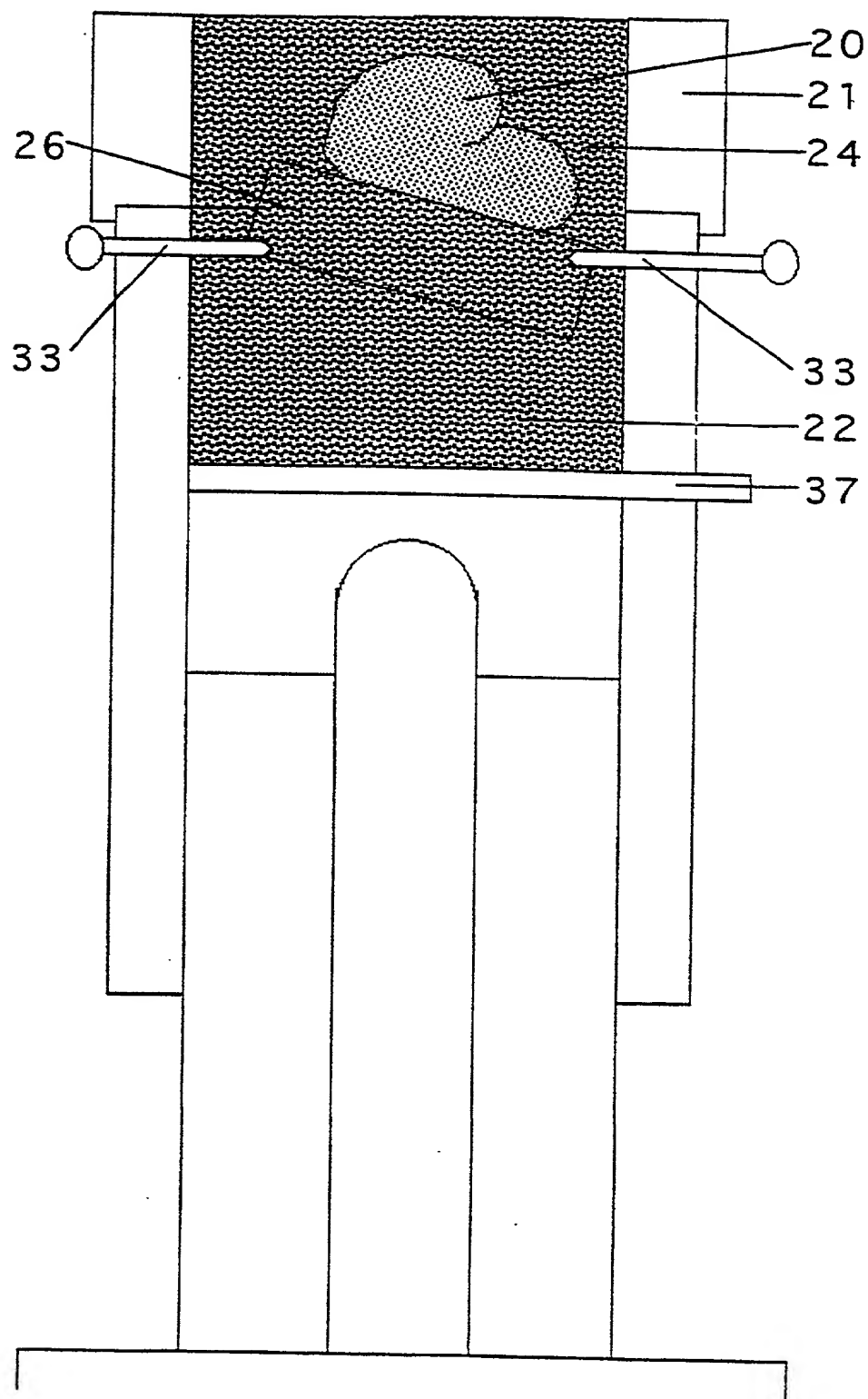
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Fig. 4e

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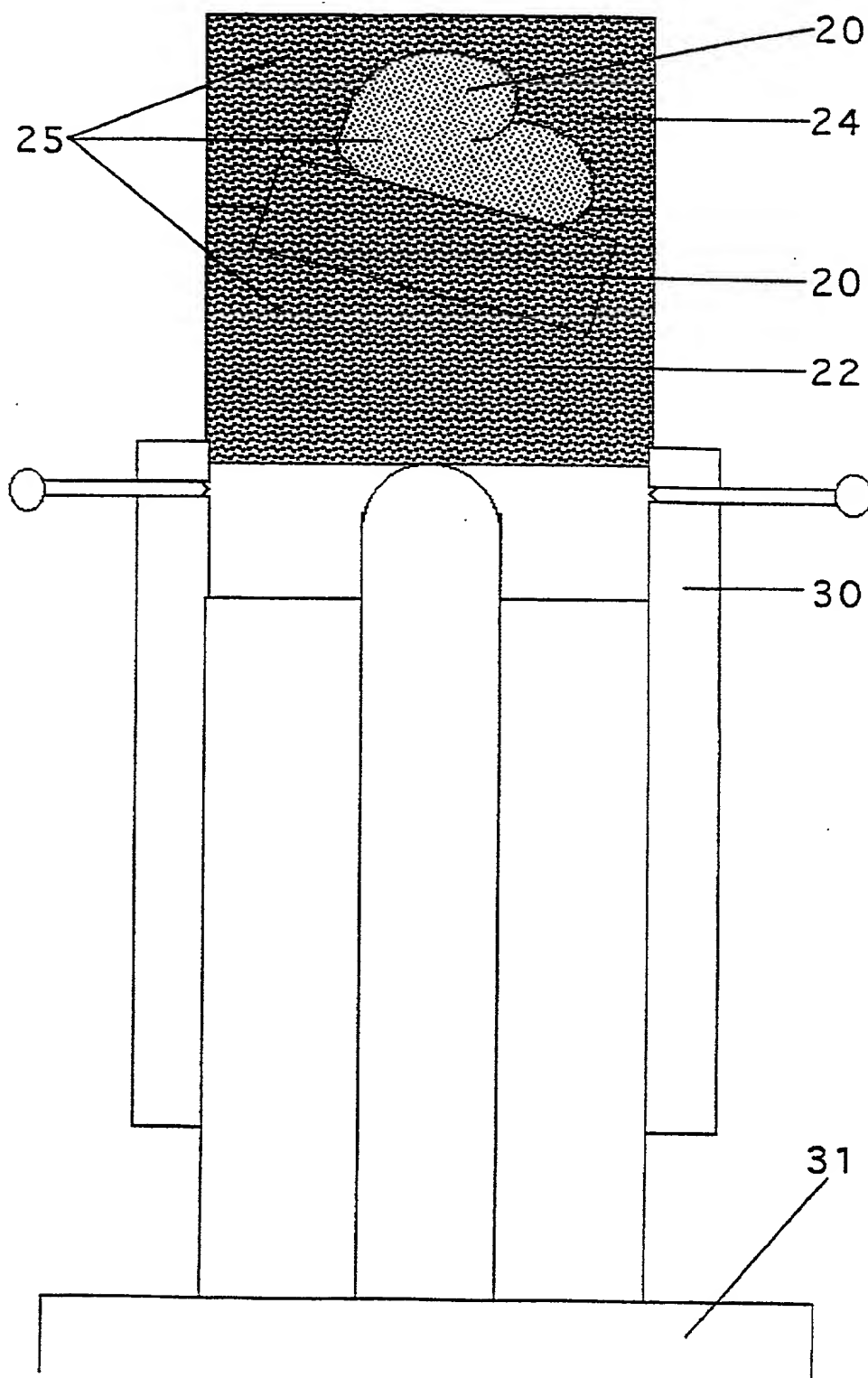
Fig. 4f



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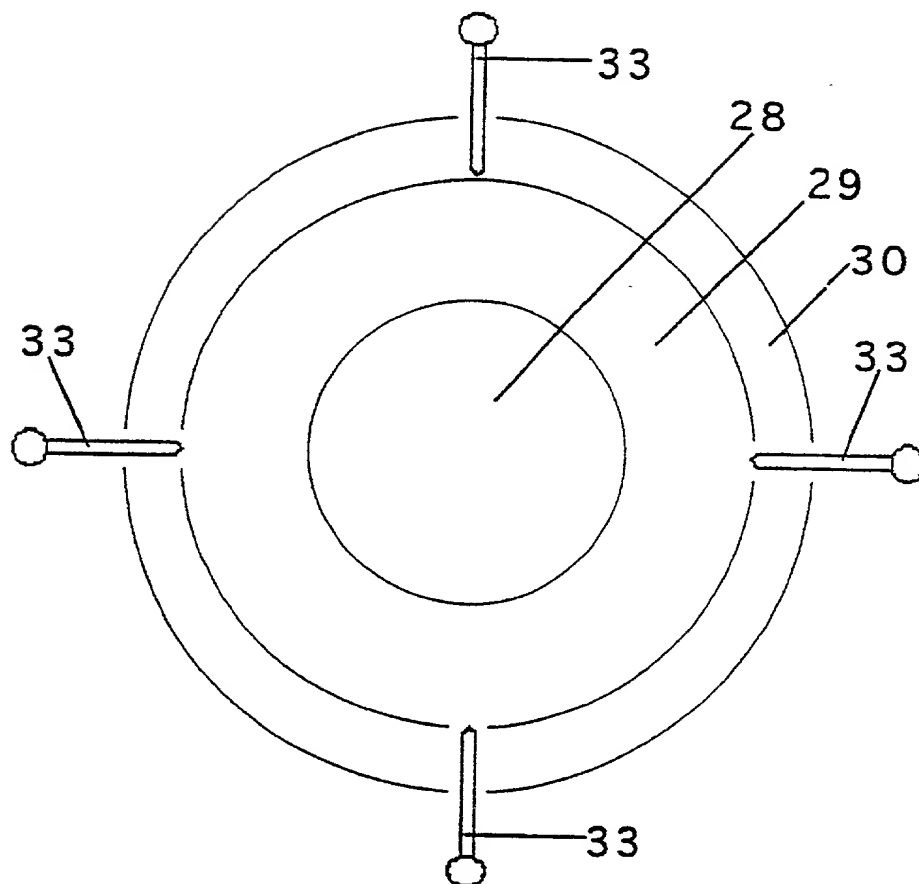
Fig. 4g



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Fig. 5



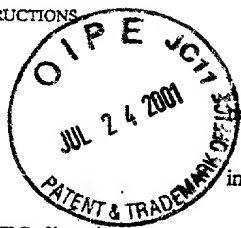
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MERCHANT & GOULD

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

* INSTRUCTIONS



As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert TITLE of invention:

A method and an apparatus for cutting of tissue blocks

Check a or b

The specification of which

a. ☐ is attached hereto

b. ☒ was filed on 8 June 2001

If "b" checked, complete

as application serial no. _____

and was amended on _____ (if applicable)

If PCT Application

(in the case of PCT-filed application)

Insert Int. application
number & filing date

described and claimed in international no. PCT/DK99/00720 filed 20 December 1999

and as amended on 21.02.2001 (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a). (Reprinted on back side).

I hereby claim foreign priority benefits under Title 35, United States Code, § 19/365 of any foreign application(s) for patent of inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

Prior applications
Check a or b

a. ☐ no such applications have been filed.

b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
Denmark	PA 1998 01699	21.12.1998	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)

If "b" checked, complete

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

For Continuation-in-Part
(CIP) Applications, complete

U.S. APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

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Epp Ryan, Sandra	Reg. No. 39,667	McKenzie, Denise L.	Reg. No. P-43,790	Wood, Gregory B.	Reg. No. 28,133
Farber, Michael B.	Reg. No. 32,612	Mueller, Douglas P.	Reg. No. 30,300	Wood, William	Reg. P-42,236
Funk, Steven R.	Reg. No. 37,830	Nasiedlak, Tyler L.	Reg. No. 40,099	Xu, Min S.	Reg. No. 39,536
Glance, Robert J.	Reg. No. 40,620	Nelson, Albin J.	Reg. No. 23,650		
Golla, Charles E.	Reg. No. 26,896	Parker, Sandra M.	Reg. No. 36,233		

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Please direct all correspondence in this case to Merchant, Gould, Smith, Edell, Welter & Schmidt at the address indicated below (or if no address is specified, the first address):

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- ☐ Independence Plaza, Suite 1400; 1050 17th St.; Denver, CO 80265-0100 (Telephone No. (303) 357-1670)
- ☐ Westwood Gateway II, Suite 400; 11150 Santa Monica Boulevard; Los Angeles, CA 90025-3395 (Telephone No. (310) 445-1140)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Insert FULL name(s)
AND address(es) of
actual inventor(s)

2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
SIGNATURE OF INVENTOR 201		SIGNATURE OF INVENTOR 202		SIGNATURE OF INVENTOR 203
DATE		DATE		DATE

Each inventor must
sign & date
Note: No legalization or
other witness required
Revised 1/8/99

For Additional Inventors: ☒ Check box and attach sheet with same information, including date and signature.

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

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Ansems, Gregory M.	Reg. No. 42,264	Gregson, Richard	Reg. No. 41,804	Pytel, Melissa J.	Reg. No. 37,209
Batzli, Brian H.	Reg. No. 32,960	Gresens, John J.	Reg. No. 33,112	Reich, John C.	Reg. No. 37,703
Beard, John L.	Reg. No. 27,612	Hamre, Curtis B.	Reg. No. 29,165	Reiland, Earl D.	Reg. No. 25,767
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Farber, Michael B.	Reg. No. 32,612	Mueller, Douglas P.	Reg. No. 30,300	Wood, William	Reg. P-42,236
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Please direct all correspondence in this case to Merchant, Gould, Smith, Edell, Welter & Schmidt at the address indicated below (or if no address is specified, the first address):

- ☒ 3100 Norwest Center, 90 South Seventh Street; Minneapolis, MN 55402-4131 (Telephone No. (612) 332-5300)
- ☐ Independence Plaza, Suite 1400; 1050 17th St.; Denver, CO 80265-0100 (Telephone No. (303) 357-1670)
- ☐ Westwood Gateway II, Suite 400; 11150 Santa Monica Boulevard; Los Angeles, CA 90025-3395 (Telephone No. (310) 445-1140)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Insert FULL name(s)
AND address(es) of
actual inventor(s)

204	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
205	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
206	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
SIGNATURE OF INVENTOR 201		SIGNATURE OF INVENTOR 202		SIGNATURE OF INVENTOR 203
DATE		DATE		DATE

Each inventor must
sign & date

Note: No legalization or
other witness required

Revised 1/8/99

For Additional Inventors:

Check box and attach sheet with same information, including date and signature.

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is cancelled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim;

or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application;

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.